THE AORTA: BUILT TO LAST A LIFETIME?

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Abstract-**The pulse pressure generated by the heart is determined by the hydraulic input impedance of the circulation which, in turn is governed by the elastic properties and structural arrangement of elastin, a protein found in the arterial walls of all but the simplest vertebrates. We suggest on the basis of scaling arguments, that pulse pressure depends on the elastic properties of the protein elastin and is independent of body mass.**

Elastin which, unlike other proteins has a turnover rate close to zero, undergoes fatigue failure in arteries due to cyclic stress, becoming progressively fragmented with age and gradually being replaced by much stiffer fibrous tissue. These changes are well advanced after 1 billion heartbeats, by which time most animals, whatever their size or heart-rate, are nearing the end of their lives. In man this number is achieved by the age of 30 years, which from an evolutionary point of view, is close to the end of useful life. The progressive failure of elastin with age and the consequent increase in arterial stiffness leads to an inexorable rise in blood pressure.

Epidemiological investigations have found that raised blood pressure in middle age is associated with impaired fetal growth. Animal experiments have shown that rats whose mothers were deprived of protein while pregnant (to simulate intra-uterine growth retardation) have stiffer aortas which contain less elastin.

Thus elastin in the aortas of individuals who are destined to become hypertensive as they age will undergo fatigue failure sooner than their normotensive counterparts. Over a lifetime, such changes will predispose to higher levels of blood pressure, increased left ventricular mass and generalized cardiovascular disease.

Keywords - Fetal programming, blood pressure, arterial elasticity, scaling, elastin

FACTORS DETERMINING PULSE PRESSURE

The structure of the vascular system has evolved to optimize the supply of oxygen and nutrients to the visceral organs, skeletal muscle and the brain. In all but the most primitive vertebrates a closed circulation provides the means to supply the body with oxygen and nutrients by convective flow, driven in a pulsatile manner by one or more hearts, thus allowing their rapid distribution throughout the body. Diffusive flow of oxygen and nutrients, at a much slower rate, is required only to allows them to complete the last few micrometers of their journey from the capillaries to the cells at their destination [1].

Pulse pressure at a given position in the arterial system is determined, in the absence of wave reflections, by the hydraulic input impedance of the circulation downstream from that point. The input impedance (Z_c) depends on arterial distensibility and cross sectional area according to the relation:

$$Z_c = k_1(Eh/r)^{0.5}.(a)^{-1} \qquad (1)$$

Where E is the circumferential elastic modulus (defined at physiological strains) of an artery of midwall radius r, thickness h and lumen cross sectional area a.

It is known that aortic cross sectional area scales with body mass according to the power law [2]:

$$a = k_2M^{0.82} \qquad (2)$$

There is evidence [3] that cardiac output is related to body mass by in a similar manner:

$$Q = k_3.M^{0.81} \qquad (3)$$

Since pulse pressure (P) is related to characteristic impedance by the relation

$$\Delta P = \Delta Q.Z_c, \qquad (4)$$

where the magnitude of the flow pulse is Q, it follows from (1), (2) and (3) that

$$\Delta P = K.(Eh/r)^{0.5} \qquad (5)$$

assuming that pulsatile flow and mean flow scale with body weight in the same manner.

Wolinsky and Glagov have clearly shown that the ratio of wall thickness to internal radius in the aorta is independent of body mass [4]. Values of E from the many studies in the literature (see [5] for a useful review) vary between approximately 0.3 and 1 MPa when measured at physiological levels of strain. However it should be noted that this includes animals which vary in weight from a few tens of grams (the rat) to 10^7g (the fin whale) and that there appears to be no systematic dependence of E on body weight. The structural basis for this invariance is, of course, the lamellar unit structure of the aorta which is found not only in all mammals but also in the other vertebrate classes [6]. If we accept that, to a first approximation at least, E is invariant with body weight it follows from (5) that pulse pressure too is independent of body weight and depends primarily on the combined effects of material stiffness and relative wall thickness. Figure 1 shows that, in the rat at physiological pressures, the elastic properties of the aorta are strongly dependent on the properties of elastin since, in all but the oldest animals, less than 10% of the collagen fibres are bearing stress. Assuming that these values for the rat aorta are representative of other mammals (there is indirect evidence that this is the case for the pig [7] and the fin whale [8]) we conclude that pulse pressure is governed by the elastic properties and structural arrangement of elastin, a protein found in the arterial walls of all the vertebrates with a closed circulation.

In contrast to the turnover of most other proteins, the replacement rate of elastin in man is effectively zero [10]. Therefore arterial elastin, which cannot be regenerated in adults shows signs of fatigue failure, becoming progressively

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Abstract

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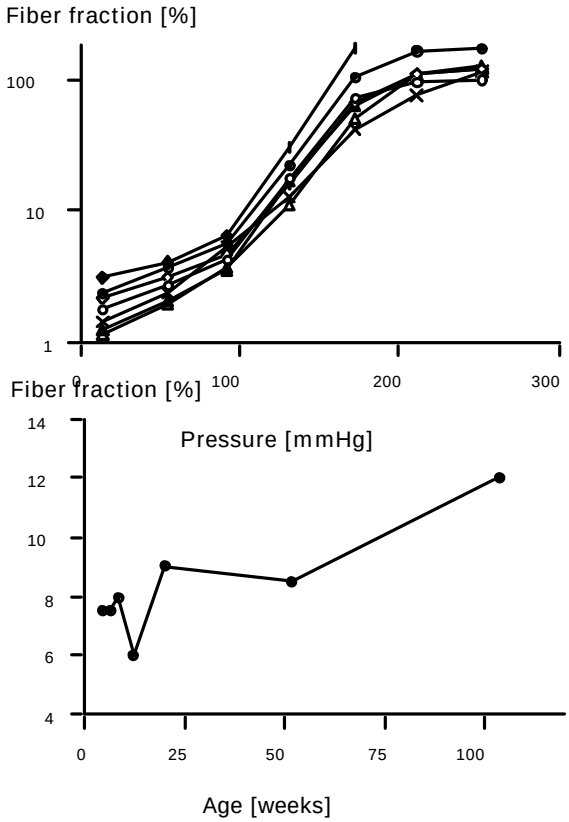

Fig. 1, upper panel. The effect of pressure on the fraction of collagen fibres bearing stress in the aorta of rats aged between 4 and 104 weeks. Lower panel, fraction of collagen fibres bearing stress at the systolic blood pressure of each age group. (Data from [9])

fragmented with age and gradually being replaced by much stiffer fibrous tissue [11, 12]. In most mammals, whatever their size or heart rate, the fragmentation is well advanced after 1 billion heartbeats, by which time they are nearing the end of their lives. In man this number is achieved by the age of 30 years, which from an evolutionary point of view, is close to the end of useful life, although for reasons which are not fully understood, human life-span is more than double this number.

To our knowledge there are no reports in the literature concerning the fatigue properties of elastin. Recent (unpublished) data from our laboratory shows that over a limited range of strains the number of cycles to failure of elastin from the nuchal ligament of the sheep (a tissue that contains approximately 80% elastin) is approximately 5 times greater than a typical natural rubber, (fig. 2), although it appears that the shape of relationship is similar, at least over the range of strains so far examined.

The increase in stiffness due to the replacement of elastin by collagen leads, as shown by (5) above, to an inexorable rise in pulse pressure with age, which in turn results in increased load on the heart and impaired cardiac function. The increased pulse pressure is amplified as the pulse propagates towards peripheral muscular arteries contributing to their hypertrophy and a consequent increase in their response to vasoconstrictors and reduction in lumen at normal values of resting smooth muscle tone. This causes mean pressure to rise which in turn results in a further decrease in the compliance of the conduit arteries due to their elastic non-linearity. Thus a positive feedback loop is established which tends to maintain increased mean and pulse pressure. It should be emphasized that these mechanical factors act in concert with metabolic blood pressure control systems such as the renin-angiotensin system.

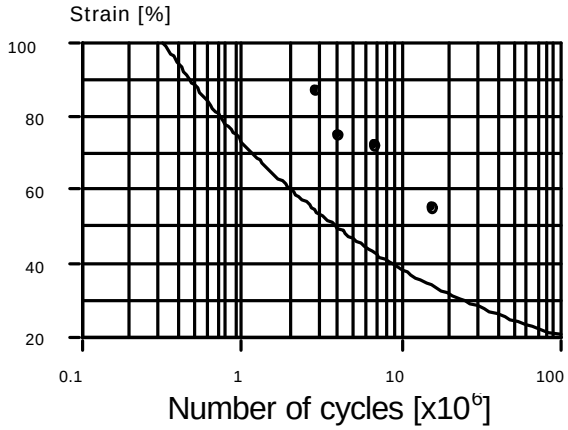

Fig. 2. The relationship between maximum strain and number of cycles to failure for a typical rubber (solid line, redrawn from [13]) and ovine nuchal ligament (points, unpublished data).

If we accept the proposition that the increases in mean and pulse pressure with age are an inevitable consequence of the fatigue failure of elastin which spares no one, the question arises: why do some people have higher blood pressure than others?

FETAL PROGRAMMING OF CARDIOVASCULAR DISEASE

There is now extensive epidemiological evidence that coronary heart disease [14], stroke [15], hypertension [16] and atherosclerosis [17], are associated with impaired growth and development during fetal life and infancy. It has been suggested that these diseases may be consequences of 'programming', whereby a stimulus or insult at a critical period of early life, often when rates of growth are maximal, leads to irreversible changes in structure and function of target organs [18]. The evidence linking impaired growth in fetal life with raised adult blood pressure is particularly strong [19], although little is known about the mechanisms that underlie this epidemiological association.

As a possible explanation for the association between fetal growth retardation and hypertension in adulthood, we have proposed that in fetuses whose growth is retarded, there is a reduction in the synthesis of elastin during the development of the conduit arteries which leads to permanent changes in their mechanical properties [20]. We suppose that the initiating event is a reduction in the rate of elastin synthesis at a time before birth when the rate is normally maximal [21]. As a result of this deficiency in elastin, the large arteries will be stiffer than normal. Decreased conduit artery compliance leads to increased pulse pressure thus imposing a greater than normal load on the left ventricle, resulting in left ventricular hypertrophy, impaired coronary arterial perfusion, hypertrophy of the arterial wall, increased peripheral resistance and a consequent increase in mean blood pressure as well. Once established, the elastin deficiency cannot be corrected due, as mentioned above, to the extremely low turnover of this protein and also, to the tendency for vascular smooth muscle preferentially to synthesize collagen when abnormally stretched [22].

Once the conduit arteries start to become stiffer their characteristic impedance and hence the pulse pressure for a given mean pressure will increase. Indeed there is evidence from studies in the rat that pulse pressure alone may be a determinant of vascular structure [23]. Increased pulse pressure will result in

increased circumferential stretch and a tendency to synthesize more collagen as well as in a generalized hypertrophy of the vessel wall, which causes a further increase in stiffness. To some extent the process will be self limiting since, as the wall becomes stiffer, the stretch due to a given pressure will be reduced. Nevertheless a positive feedback loop is again established which tends to maintain a high pressure following its initiation by the body's limited ability to synthesize elastin. Over time, the gradual fragmentation and loss of elastin that accompanies aging (see above) and its replacement with collagen will tend further to amplify the increase in blood pressure.

EXPERIMENTAL EVIDENCE FOR THE PROPOSED MECHANISM

In a previous study of arterial dimensions post mortem static elasticity and scleroprotein content on rats aged 4 weeks whose mothers had been given a low protein diet (9%) [24] while pregnant (to simulate intra uterine growth retardation in man) we found, as others had previously, that systolic blood pressure in the caudal artery was significantly greater than that of control animals whose mothers had been fed an isocaloric diet containing 18% protein. In spite of normal body weight and aortic lumen diameter, medial cross sectional area was significantly reduced and material stiffness (circumferential incremental elastic modulus) were increased, while elastin content relative to dry weight was decreased. These observation were consistent with the hypothesis that growth retardation in utero results in stiffer aortas containing less elastin and that, as a consequence, pulse pressure and cardiac load are increased.

We have now extended these measurements to pubescent and young adult animals and briefly report the results of a comparison between the three age groups.

In summary we observed the following: (see table I for details)

- The weights at death of the 4 and 8 week animals did not differ significantly from their control counterparts although at birth the LP animals in all three age groups were significantly lighter. Thus in the two younger LP groups there were signs of 'catch up growth'. By the age of 12 weeks however, the LP animals were significantly lighter than controls, suggesting growth impairment in the longer term.
- In spite of evidence of hypertension (raised systolic blood pressure in the 4 week animals and left ventricular hypertrophy in the older groups (BP not measured), all LP groups had significantly reduced medial area when compared to controls. This observation was surprising because, in other models of experimentally induced or spontaneously occurring hypertension, the aortic media invariably becomes hypertrophied. However the LP animals do not appear to respond in this way.
- Material stiffness measured at a circumferential strain of 30% (incremental elastic modulus) was significantly increased in the 4 and 12 week LP animals but not in the 8 week group. There were no significant differences in functional stiffness (Peterson Modulus) between the control and LP groups at any age.
- Elastin content relative to the dry weight of the vessel was significantly increased in the 4 and 12 week LP animals but not in the 8 week group. Diet had no significant effect on collagen content.

TABLE 1.

Mean values (± SEM) of animal weights, aortic dimensions and static elastic modulus. For low protein (LP) and control animals killed at the ages of 4, 8 and 12 weeks. There were between 8 and 11 animals in each age and treatment group.

Variable	Age (week)	LP	Control	P ("t" test)
Body weight at death (g)	4	118 ± 4	99 ± 7	NS
	8	228. ± 13.3	223. ± 4.25	NS
	12	462 ± 10	557. ± 13.3	<0.05
Medial cross-sectional area [mm^2]	4	0.40 ± 0.01	0.42 ± 0.01	<0.05
	8	0.55 ± 0.03	0.77 ± 0.05	<0.01
	12	1.49 ± 0.12	1.77 ± 0.12	<0.01
Peterson modulus [$Nm^{-2} \times 10^4$]	4	7.37 ± 0.46	7.34 ± 0.56	NS
	8	6.04 ± 0.46	7.74 ± 0.56	NS
	12	7.48 ± 0.43	6.67 ± 0.33	NS
Incremental modulus [$Nm^{-2} \times 10^5$]	4	8.86 ± 1.36	6.71 ± 0.99	<0.05
	8	4.63 ± 0.57	4.97 ± 0.99	NS
	12	4.50 ± 0.45	3.42 ± 0.53	<0.05
Medial elastin [%]	4	46.8 ± 2.78	57.2 ± 3.72	<0.01
	8	61.8 ± 1.05	63.2 ± 0.77	NS
	12	60.0 ± 1.21	64.4 ± 0.75	<0.05
Medial collagen [%]	4	15.4 ± 1.11	17.0 ± 1.53	NS
	8	22.6 ± 1.23	25.4 ± 2.13	NS
	12	25.2 ± 1.23	27.4 ± 1.00	NS

CONCLUSIONS

The evidence presented here suggests that the structure and elasticity of conduit arteries in pre-pubertal and young adult rats is strongly affected by maternal diet in early life. These changes are consistent with the hypothesis that elastin, by determining arterial stiffness and therefore the relationship between pulse pressure and flow, provides at least in part, an explanation for the link between in utero growth retardation and hypertension. We are not yet able to explain the anomalous results of the 8 week age group. We speculate that they may be due to metabolic and structural changes associated with puberty.

It has been shown that elastin synthesis in the mouse occurs only while the aorta is growing and that it is effectively complete by the age of 4 weeks [25, 26]. Any change in its rate of synthesis during this critical period is therefore likely to have a lasting effect. It remains to be seen if the rate of elastin synthesis is reduced in animal models of growth retardation and if the observed reduction in aortic elastin content in our rat model is a cause or a consequence of the associated hypertension.

Although after a lifetime of cyclic stress the aorta shows clear signs of degeneration it is clear that, in individuals who were well nourished in early life, the heart is able to maintain an adequate output in spite of a steady increase in its load.

If, as now seems possible, there is a connection between reduced elastin synthesis in utero and essential hypertension in adulthood, this may provide the basis for a new approach to the treatment and prevention of one of the major causes of morbidity and mortality in the developed world.

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